...IGF-1 Deficiency due to GH insensitivity: ...ears of experience.

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...tural growth is improved ...combinant human (rh)IGF-1 in ...cy (IGFD) resulting from ...mone (GH) Most of these reports, ...results on small numbers of children ...for brief intervals We now report the safety ...65 children with IGFD treated for up to 10 5 years (median 3 5 years)

METHODS

The key inclusion criteria for this multi-center, open label study were

- Age ≥2 years
- Open epiphyses
- Height SDS< –2
- Height velocity <50th percentile
- Serum IGF-1 SDS< –2

Of 39 boys and 26 girls, 56 are diagnosed with GH receptor defects (Laron syndrome), 7 developed growth-attenuating antibodies to GH following GH therapy, and 2 have GH insensitivity of unknown etiology All had profound growth failure at enrollment, with a mean height standard deviation score of -6 5 (range, -10 7 to -2 8) [Table 1] Mean (± SD) age at start of treatment was 7 1 ± 4 0y (range, 1 7 to 16 2y)

Initially, dose selection was achieved by titration to tolerance (avoidance of hypoglycemia) Individualization of dose continued to occur based on safety and efficacy considerations rhIGF-1 from Genentech, Inc was used throughout Subjects received 80-120 µg/kg rhIGF-1 twice daily by subcutaneous injection

Table 1. Baseline Characteristics of the Study Population (n=65)

	Mean	SD	Range
Age (years)	7 1	4 0	1 7 to 16 2
Height (cm)	86 7	17 0	61 3 to 133 1
HT-SDS	-6 5	1 7	-10 7 to -2 8
IGF-1[1] (ng/mL)	33 0	11 8	0 2 to 74
GH[1,2] (ng/mL)	57 6	47 8	7 to 204

[1] n = 50
[2] unstimulated sample

RESULTS

Patient Disposition

Of the 65 patients in the analysis

- 3 completed therapy
- 4 were discontinued for non-compliance
- 4 were lost to follow-up
- There were no patient withdrawals due to adverse events
- There were no deaths

Adverse Event Reporting

Forty-four of the 65 subjects (68%) reported at least one adverse event (AE) [Table 2]. Most AEs were reported as not related to therapy, and consisted of illnesses and injuries commonly occurring in otherwise healthy children

Table 2. Adverse Events by System Organ Class

Adverse Events	Number of Subjects (%)
Subjects Enrolled	65 (100%)
Subjects Reporting At Least One Adverse Event	44 (68%)
Metabolism and Nutritional Disorders	33 (51%)
Respiratory, Thoracic and Mediastinal Disorders	27 (42%)
Infections and Infestations	26 (40%)
General Disorders and Administration Site Conditions	25 (39%)
Nervous System Disorders	23 (35%)
Gastrointestinal Disorders	22 (34%)
Ear and Labyrinth Disorders	21 (32%)
Musculoskeletal and Connective Tissue Disorders	18 (28%)
Skin and Subcutaneous Tissue Disorders	17(26%)
Investigations	17(26%)
Blood and Lymphatic System Disorders	16 (25%)
Surgical and Medical Procedures	12 (19%)
Eye Disorders	11 (17%)
Injury Poisoning and Procedural Complications	9 (14%)
Cardiac Disorders	8 (12%)
Congenital Familial and Genetic Disorders	8 (12%)
Psychiatric Disorders	8 (12%)
Renal and Urinary Disorders	8 (12%)
Reproductive and Breast Disorders	7 (11%)
Neoplasms Benign Malignant and Unspecified	1 (2%)*
Endocrine Disorders	1 (2%)
Social Circumstances	1 (2%)
Vascular Disorder	1 (2%)

* Warts on toe

Some AEs were reported as both frequent (>10%) and related to rhIGF-1 therapy [Table 3] Hypoglycemia was documented in 26 subjects (40%) during treatment, whereas only 12 subjects (18%) had hypoglycemia documented prior to treatment Hypoglycemia occurred more frequently in younger children During treatment, symptomatic hypoglycemia was generally avoided when a meal was consumed shortly after injection of the rhIGF-1

Table 3. Adverse Events

Adverse Event	Number of Subjects (%)
Hypoglycemia	26 (40%)
Tonsillar hypertrophy	10 (15%)
Snoring	16 (25%)
Tonsillectomy/adenoidectomy	3 (4 6%)
Middle ear effusions	5 (8%)
Abnormal tympanometry	16 (25%)
PE tube placement	8 (12%)
Intracranial hypertension	3 (4 6%)
Lipohypertrophy	21 (32%)

- Some events may be inter-related, reflecting rhIGF-1 induced growth of lymphoid tissue including tonsillar hypertrophy, snoring, middle ear effusions, and abnormal tympanometry or audiograms [Table 3]
- Intracranial hypertension (IH) occurred in twin siblings with nausea, vomiting and papilledema that resolved quickly without alteration of therapy, rhIGF-1 treatment was discontinued in another child with IH, and was resumed at a lower dose without recurrence
- Lipohypertrophy at the injection sites was always associated with a lack of proper distribution of injections and occurred in 32% of the patients
- Increase in size of the kidneys and spleen by ultrasound occurred in the first 2-3y of therapy but no adverse changes of renal function were observed
- There were no deaths and no cases of neoplasia

CONCLUSIONS

Long-term treatment with rhIGF-1 in children with IGF-1 deficiency appears to be well tolerated and has an acceptable safety profile in children with GH insensitivity

See poster P3-451 for efficacy data from this study

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